HPV ROBUST SUMMARIES

FOR

201-13195

BUTYLATED TRIPHENYL PHOSPHATE

CAS No. 220352-35-2

March 4, 2004

Submitted By:

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1. Substance Information

CAS Number:	220352-35-2
Chemical Name:	Butylated triphenyl phosphate
Physical State:	Liquid
Purity:	75-85%
Impurity:	triphenyl phosphate (CAS No. 204-112-2)
Synonyms:	t-butylphenyl diphenyl phosphate t-butylphenyl phenyl phosphate
Commercial Products:	Phosflex 51B, Phosflex 61B, Santisizer 154, Fyrquel GT, SYN-O-Ad 8485, and Durad 220B consist primarily of t-butylphenyl phenyl phosphate esters
Uses:	Used in plastics, lubricants, and hydraulic fluids
Exposure Limits:	None

2. Physical – Chemical Properties

2.1 Boiling Point:

Identity:	Phosflex 61B (Lot No. 0161K0103)
Method:	OPPTS 730.7220
Year:	2003
GLP:	Yes
Value:	>400°C
Conclusion:	The boiling point of Phosflex 61B is > 400°C
Reliability:	1
Reference:	1

2.2 Vapor Pressure:

Identity:	Phosflex 61B (Lot No. 0161K0103)
Method:	OPPTS 730:7950
Year:	2003
GLP:	Yes
Value:	1.08 v 10^{-3} Pa at 20°C

Conclusion: The vapor pressure of Phosflex 61B is 1.08 x 10^{-3} Pa @ 20°C.
Reliability: 1
Reference: 29

2.3 Density/Specific Gravity

Identity: Butylated triphenyl phosphate
Method: OPPTS 830.7300
Year: Not known
GLP: No
Value: 1.18 @ 25°C
Conclusion: The density of butylated triphenyl phosphate is 1.18 @ 25°C.
Reliability: 4
Reference: 2

2.4 Water Solubility

Identity: Butylated triphenyl phosphate
Method: OECD 105
Year: 2001
GLP: No
Value: 0.04 mg/l @ 25°C
Conclusion: The water solubility of butylated triphenyl phosphate is 0.04 mg/l @ 25°C
Reliability: 2
Reference: 3

2.5 Octanol:water Partition Coefficient

Identity: Phosflex 61B (Lot No. 0161K0103)
Method: OPPTS 830.7550
Year: 2003
GLP: Yes
Value: Log Kow = 4.85 @ 25°C
Conclusion: The n-octanol:water partition coefficient (log Kow) was determined to be 4.85 @ 25°C.
Reliability: 1
Reference: 4

2.6 Flash Point

Identity: Butylated triphenyl phosphate

Method:	Pensky-Martens Closed Cup
Year:	Not known
GLP:	No
Value:	246.1°C
Conclusion:	The flash point is 246.1°C
Reliability:	2
Reference:	5

3. Environmental Fate

3.1 Photodegradation

Identity:	Santicizer 154 (Lot No. 1802928)
Guideline:	MIC Environmental Method for Sunlight Photolysis Studies
Year:	1981
GLP:	Yes
Light source:	Sun light
Method:	The test substance was evaluated for photodegradation in both natural water (Mississippi river water)and purified water. Four tubes were used for zero time analysis, eight tubes were mounted for direct sunlight exposure, and eight tubes were used as the dark controls. During direct sunlight exposure, the average maximum temperature was 28 degrees C and the average minimum was 18 degrees C. The concentration of the test substance was 10 mg/l. The water was sampled on days 2, 5, 9, and 14. Water samples were extracted with hexane and analyzed by gas chromatography using a nitrogen-phosphorus selective detector. Blank water samples were run concurrently.
Results:	There is no detectable direct or sensitized photolysis or non-photolytic losses during the 14 day test period. These results indicate that neither photolysis nor chemical transformation processes such as hydrolysis are likely to be significant in an aqueous environment.
Conclusion:	Under the conditions of this test, the half-life was greater than 14 days.
Reliability:	1
Reference:	6

3.2 Stability in Water

Identity:	Phosflex 61B (Lot No. 0161K0103)
Guideline:	OPPTS 835.2110 and OECD 111
Year:	2004
GLP:	Yes
Method:	A preliminary hydrolysis study was conducted in which Phosflex 61B was maintained in buffered water at pH 4, 7, and 9, at 50°C, for five days. Day

0 and day 5 waters were analyzed by LC/MS/MS to determine the total amount of test substance present. Calibration curves were used to assure accurate quantitation. The pH 4 buffer consisted of potassium hydrogen phthalate, the pH 7 buffer potassium dihydrogen phosphate, and the pH 9 buffer contained boric acid and potassium chloride. Because hydrolysis was observed at 50°C in the preliminary study at all three pH, a definitive hydrolysis test was conducted at pH 4, 7, and 9, over a 30 day period, at 15°C and at 25°C, using the same buffer systems. LC/MS/MS was also used in the definitive study to determine hydrolysis of the test substance. Test substance was measured at 10 sampling intervals within the 30 days.

Results: Hydrolysis of Phosflex 61B occurred at all 3 pH. The approximate half-lives for Phosflex 61B at 25°C at pH 4, 7, and 9 are 60, 14, and 5.4 days, respectively. At 15°C, the half-lives at pH 7 and 9 are approximately 28 and 15 days, respectively. The half-life at pH 4 is greater than 100 days.

Conclusion: Phosflex 61B hydrolyzes in water at all three pH.

Reliability: 1

Reference: 30

3.3 Biodegradation

Identity: Santicizer 154 (Lot No. KL04105)

Guideline: OECD 301A Die-Away Test for Biodegradation

Year: 1982

GLP: Yes

Method: This study utilized the river die-away test method which measures the die-away or decrease in concentration of the test substance over time in Mississippi River water maintained in sealed bottles. River water was collected, transferred to a 5 gallon glass carboy, and aerated until placed on test. Replicate solutions contained either 50 or 500 ppb of the test substance. Fifteen bottles of each concentration contained the active river water whereas five bottles at each concentration contained membrane-filtered water. In addition, five bottles containing river water and 500 ppb test substance were autoclaved. All sample bottles were kept in the dark at ambient temperature (24 degrees C). Samples were analyzed at preset times. Bottles containing just river water were prepared and used to assay the microbial population. Quadruplicate plates were enumerated after incubation for 48 hours at 35 degrees C. The amount of test substance present was determined by a gas chromatography method using a nitrogen-phosphorus selective detector.

Results: The half life of the butylated triphenyl phosphate in the spiked water samples was less than 0.5 days for both the 50 ppb and the 500 ppb samples in river water. The material was so rapidly lost that there were insufficient numbers of data points for use in the statistical method of half life analysis. In contrast, the half life in the autoclaved water was about 39

	days. This indicates that biotransformation is the important process for the degradation of butylated triphenyl phosphate, and that contribution from hydrolysis or from other physical processes were not significant. Degradation in the membrane-filtered water was still relatively rapid, primarily because of bacterial contamination.
Conclusion:	Butylated triphenyl phosphate is rapidly biodegraded by the microorganisms present in river water. It does not rapidly hydrolyze or decompose in the absence of organism capable of biotransforming the substance.
Reliability:	1
Reference:	7

4. Ecotoxicity

4.1 Acute Toxicity to Fish

Identity:	Fyrquel GT (Lot No. 4688, representative sample of commercial product)
Guideline:	EPA Methods for Toxicity Testing with Aquatic Organisms, EPA 660/3-75-009, 1975
Year:	1979
GLP:	No
Species:	Salmo gairdneri (Rainbow Trout)
Method:	Groups of rainbow trout were exposed to one of five concentrations (1.3, 2.5, 5.0, 10.0, and 20.0 mg/l) of the test substance. The water was analyzed to assure correct pH, dissolved oxygen, hardness, alkalinity, and other parameters. A non-treated control group was included in the study. Ten fish per group were exposed for 96 hours in a flow-through system. The LC50 and 95% confidence limits were calculated using the Spearman-Karber method. The fish were observed daily for abnormal behavior which was recorded.
Results:	The water analysis showed a pH of 8.08, total hardness of 216 mg/l as $CaCO_3$, total alkalinity of 146 mg/l as $CaCO_3$, and specific conductance of 495 umhos/cm. The water temperature was maintained at 10°C. The 96 hour LC50 was calculated to be 13.7 mg/l with 95% confidence limits of 12.0 to 15.8 mg/l. The 96 hour NOEC is 2.5 mg/l. Higher doses produced various behavioral signs, including quiescence, irritation, erratic swimming, and labored respiration. These symptoms were more severe in the higher dose groups, demonstrating a dose-response relationship.
Conclusion:	The 96 hour LC50 = 13.7 mg/l and the NOEC = 2.5 mg/l.
Reliability:	2
Reference:	8

Identity:	SYN-O-Ad 8485 (Lot No. 5170E-6)
Guideline:	OECD 203
Year:	1996

GLP:	Yes
Species:	Cyprinodin variegatus (Sheepshead Minnow)
Method:	Groups of sheepshead minnow were exposed to either 0, 0,13, 0.22, 0.36, 0.60, or 1.0 mg/l of SYN-O-Ad 8485 for 96 hours, in a static-renewal system. The water was analyzed for salinity, hardness, pH, and other parameters. The fish were observed for mortality, morbidity, and signs of toxicity. There were 10 fish per treatment level.
Results:	Analysis of the water showed salinity at 30%, pH of 8.0, and temperature maintained at 22°C. The 96 hour LC50 was determined to be greater than 1.0 mg/l, the highest concentration tested. The NOEC was 1.0 mg/l. There were no signs of toxicity, and there was no mortality during the conduct of this study.
Conclusions:	The 96 hour LC50 > 1.0 mg/l and the NOEC + 1.0 mg/l.
Reliability:	1
Reference:	9

4.2 Acute Toxicity to Aquatic Invertebrates

Identity:	SYN-O-Ad 8485 (Lot No. 5170E-6)
Guideline:	OECD 202, part 1 "Daphnid sp., Acute Immobilization Test"
Year:	1996
GLP:	Yes
Species:	Mysidopsis bahia
Method:	A preliminary rangefinding test was conducted to determine the solubility of the test substance in seawater and to identify appropriate dose levels. Since 100% mortality was obtained at 1.0 mg/l nominal concentration and lethergy was observed at nominal 0.5 mg/l, the doses chosen for the definitive tests were nominal concentrations of 0.13, 0.22, 0.36, 0.60, and 1.0 mg/l. In the definitive test, the pH, salinity, dissolved oxygen concentration, and temperature were measured. The comparative measured concentrations were 0.093, 0.090, 19, 0.50, and 0.23 mg/l. Analysis of quality control samples resulted in measured concentrations which ranged from 97.2 to 120% of the nominal concentrations. Mysids were observed daily for behavior anomalies. Exposure for 96 hours. Twenty mysids per treatment level, two replicate vessels per dose.
Results:	The natural filtered seawater had a pH of 7.9, salinity of 24%, and was maintained at 25°C. Throughout the exposure period, there was no visible sign of undissolved test substance (e.g., no precipitate, surface film) in any of the exposure solutions. The high nominal dose of 1.0 mg/l caused 100% mortality. At 96 hours, the 0.36 and 0.60 mg/l exposure concentrations caused 40 and 95% mortality, respectively. No mortality or sublethal effects were observed in the mysids exposed to mysids exposed to either 0.13 and 0.22 mg/l. The 96 hour LC50 was calculated by probit analysis to be 0.39 mg/l, with 95% confidence interval of 0.34 to 0.44 mg/l. The NOEC was found to be 0.22 mg/l.

Conclusions: The 96 hour LC50 = 0.39 mg/l and the NOEC = 0.22 mg/l.
Reliability: 1
Reference: 10

4.3 Toxicity to Aquatic Plants

Identity: S-154 (Lot No. BN-79-1384328-2a)
Guideline: EPA Alga Assay Procedure: Bottle Test. 1971.
Year: 1979
GLP: No
Species: Selenastrum capricornutum
Method: The phytotoxicity of the test substance was determined in the freshwater green alga, Selenastrum capricornutum, over a period of 96 hours. Doses used in this definitive test were based on the results of a rangefinding test. The measured endpoint is a decrease in chlorophyll in the treated cultures as compared to the control cultures. The second endpoint measured is the concentration that causes a 50% decrease in cell number. Triplicate cultures were used for all test concentrations and for the control group. Chlorophyll was measured fluorometrically. Cells were counted with a hemocytometer and a microscope. Temperature was maintained at 24°C.
Results: Based on a decrease in the amount of chlorophyll present, the 96 hour EC50 was determined to be 3.0 ppm with 95% confidence limits of 1.5-6.3 ppm. The calculated EC50 based on a decrease in cell number was 2.6 ppm with 95% confidence limits of 1.0-7.0 ppm. Water pH was 7.6.
Conclusions: The 96 hour EC50 = 2.6 ppm.
Reliability: 2
Reference: 11

4.4 Chronic Toxicity to Aquatic Invertebrates

Indentity: S-154 (Lot No. BN-78-1384328-3)
Guideline: EPA Protocol for Conducting Chronic Tests with the Water Flea, 1975
Year: 1979
GLP: Yes
Species: Daphnia magna
Method: Water conditions, including pH, hardness, and temperature were measured during the study. Daphnia magna were continuously exposed to five mean measured concentrations of test substance ranging from 5.1 to 100 ug/l, for a period of 21 days. A concurrent control group was included in the study. Aliquots of water were removed from each tank weekly and analyzed by gas chromatography using a nitrogen-phosphorus specific detector. Fortified water samples were used in a recovery study to determine the percent recovery of the test substance from the water.

Results: Water temperature was maintained at 22°C, total hardness at 174 mg/l as $CaCO_3$, pH at 8.3, and dissolved oxygen at 8.0 mg/l. Survival of daphnids exposed to 100 ug/l was significantly reduced when compared to survival of control daphnids when measured on days 14 and 21. Exposure concentrations as high as 40 ug/l had no effect on survival or reproduction. The average number of offspring produced per daphnid exposed to 100 ug/l was significantly less than the number of offspring produced by control daphnids. Offspring production was unaffected among daphnids exposed to all other concentrations (40, 16, 8, 5 and <2 ug/l). The NOEC for mortality and reproduction was found to be 40 ug/l.
Conclusions: The NOEC for mortality and reproduction = 40 ug/l.
Reliability: 1
Reference: 12

5. Mammalian Toxicity

5.1 Acute Toxicity

5.11 Acute Oral Toxicity

Identity: Phosflex 51B (Lot No. 4833-1-2)
Guideline: 40 CFR 798.1175
Year: 1979
GLP: No
Species: Rat
Strain: Sprague-Dawley
Method: Five male and 5 female rats were fasted for 24 hours after which they received a single 5000 mg/kg oral gavage dose of butylated triphenyl phosphate. They were observed daily for 14 days for signs of toxicity and for mortality. They were then sacrificed and necropsied. Internal structures and organs were observed for gross lesions.
Results: There was no mortality. Signs of toxicity included depression, diarrhea, and stains on the fur and around the nose. The animals' behavior and appearance returned to normal by day 6. No gross abnormalities were observed at necropsy The acute oral LD50 is greater than 5000 mg/kg.
Conclusion: The acute oral LD50 > 5000 mg/kg.
Reliability: 1
Reference: 13

5.12 Acute Inhalation Toxicity

Identity: Phosflex 51B (Lot No. 4833-1-2)
Guideline: OPPTS 870.1300
Year: 1979

GLP:	No
Species:	Rat
Strain:	Sprague-Dawley
Method:	Ten male and 10 female rats were exposed for 4 hours to an aerosol of Phosflex 51B at the highest attainable concentration, 3.1 mg/l. Aerosol concentration was determined from samples collected at the breathing zone of the rats during exposure. Analysis was by gas-liquid chromatography using a flame ionization detector. Aerosol particle size analysis was determined during the exposure period using a cascade impactor. Body weights were obtained on days 0, 3, 7, and 14. Necropsies were performed on all animals.
Results:	The 4 hour exposure to the highest attainable dose, 3.1 mg/l, produced no mortality. Particle size distribution ranged from 2.5 to 2.8 um. Ruffled fur was the only clinical sign of exposure. There was no effect on body weights. At necropsy, 1 female rat had reddened lungs and another female rat had whitish lungs. No other gross changes were noted. The acute inhalation LC50 is greater than 3.1 mg/l.
Conclusion:	The acute inhalation LC50 > 3.1 mg/kg.
Reliability:	1
Reference:	14

5.13 Acute Dermal Toxicity

Identity:	Phosflex 51B (Lot No. 4833-1-2)
Guideline:	EPA OTS 798.1100
Year:	1979
GLP:	No
Species:	Rabbit
Strain:	New Zealand White
Method:	Abdominal fur on 5 male and 5 female New Zealand White rabbits was closely clipped and the skin was abraded on half the animals. The skin on the other half of the animals was left intact. Phosflex 51B was applied neat at 2000 mg/kg to the clipped area. The animals were observed daily for 14 days following treatment, for signs of toxicity. Necropsies were conducted on day 15 on all animals. Internal organs were examined for gross lesions.
Results:	One of the ten animals died. Clinical signs in the remaining 9 rabbits included mild diarrhea and slight depression. All of the 9 animals fully recovered prior to the end of the 14 day observation period. No treatment-related lesions were observed during necropsy.
Conclusion:	The acute dermal LD50 > 2000 mg/kg.
Reliability:	1
Reference:	15

5.14 Skin Irritation

Identity:	Phosflex 51B (Lot No. 4833-1-2)
Guideline:	EPA OTS 798.4470
Year:	1979
GLP	No
Species:	Rabbit
Strain:	New Zealand White
Method:	The backs of six young adult rabbits were shaved and half the shaved areas were abraided 24 hours prior to dosing. Each animal received 0.5 ml of Phosflex 51B on the shaved area. The application sites were wrapped for 24 hours, then unwrapped at which time the remaining test substance was removed. The animals were observed for signs of skin irritation 24, 48, and 72 hours after treatment. The treated skin was evaluated for degree of irritation using the Draize scoring method.
Results:	Mild to moderate erythema was observed 24 hours after treatment. No edema was observed. At 48 hours, mild erythema was still evident at 4 dose sites. There was no irritation present at the 72 hour observation period. The primary irritation score was 0.50 indicating that Phosflex 51B is a mild dermal irritant.
Conclusion:	Phosflex 51B is a mild skin irritant.
Reliability:	1
Reference:	16

5.15 Eye Irritation

Identity:	Phosflex 51B (Lot No. 4833-1-2)
Guideline:	EPA OTS 798.4500
Year:	1979
GLP:	No
Species:	Rabbit
Strain:	New Zealand White
Method:	A dose of 0.1 ml of Phosflex 51B was placed in the everted lower left eyelid of 9 rabbits. The upper and lower lids were then held together for about one second. About 30 seconds after treatment, the treated eyes of 3 rabbits were gently flushed with water for about 1 minute. The treated eyes of the remaining 6 rabbits remained unwashed. The right eye of each rabbit served as an untreated control eye. Each treated eye was scored for irritation at 24, 48, 72, and 96 hours ad at 7 days after treatment. The eyes were scored for irritation according to the method of Draize.
Results:	Mild redness of the conjunctiva was observed in two rabbits (one with a washed eye, the other with an unwashed eye) at the 24 hour observation. The two eyes cleared by 48 hours, but another eye (unwashed) showed mild redness of the conjunctiva at 48 hours. All eyes were clear of irritation at 72 hours and 96 hours, and remained so through the 7 day

observation. The average irritation scores at 24 and 48 hours were 0.44 and 0.22, respectively.

Conclusion: Phosflex 51B is a very mild eye irritant.
Reliability: 1
Reference: 17

5.2 Repeated Dose Toxicity

Identity: Phosflex 51B (Lot No. 0065-21)
Guideline: EPA OTS 798.2650
Year: 1981
GLP: Yes
Species: Rat
Strain: Sprague-Dawley
Route: Oral (blended in diet)
Duration: 3 Months
Method: This study consisted of four groups of rats, each group containing twenty male and twenty female animals. One group was an untreated control group. The other groups received Phosflex 51B daily for three months blended into their diets, at a dose of either 100, 400, or 1600 ppm. Parameters measured during the study include body weight, food consumption, daily clinical observations, hematology, clinical chemistry, and cholinesterase activity. All animals were necropsied at the end of the 3 month exposure, at which time they were examined for gross changes. Their tissues were removed, processed through histology, and examined via diagnostic pathology.

Results: There were no treatment related effects on body weights, food consumption, hematology, clinical chemistry, or on cholinesterase values. Daily Phosflex 51B treatment for 3 months did not result in either gross or microscopic lesions or anomalies. There was a significant increase in the absolute and relative mean weights of livers in the high dose male rats, the mean relative liver weights of the high dose female animals, the mean kidney weights of the high dose male rats, and the mean absolute weights of the adrenal glands from the high dose female rats. While increases in specific absolute and/or relative organ weights in some animals, there was no corresponding increase in histopathological changes in these organs. No treatment-related alterations were seen in any of the treated animals. Since increased organ weights were observed in certain male and female rats that received the high dose, the NOEL in this study is 400 ppm

Conclusion: Phosflex 51B demonstrated low systemic toxicity when administered daily in the feed to Sprague-Dawley rats for 90 days.
Reliability: 1
Reference: 18

5.3 Genetic Toxicity

5.3.1 In Vitro Gene Mutation

Identity:	Phosflex 51B (Lot No. 4833)
Guideline:	EPA OTS 798.5265
Test Type:	Bacterial Reverse Mutation Test (Ames Test)
Year:	1979
GLP:	No
Method:	Five tester strains of Salmonella typhimurium, TA-1535, TA-1537, TA-1538, TA-98, and TA-100, were exposed to Phosflex 51B in the presence and absence of a metabolic activating system. Positive control chemicals were included in the assay, as was a solvent (DMSO) and negative control group.
Results:	The positive control chemicals significantly increased the number of revertants per plate, confirming that the assay was sensitive to, and responsive to, mutagenic chemicals. Phosflex 51B did not increase the number of revertants per plate and thus did not cause mutation in the test system, either in the presence or absence of a metabolic activating system
Conclusion:	Phosflex 51B did not express mutagenic activity in this test.
Reliability:	1
Reference:	19

Identity:	Phosflex 51B (lot No. 4833)
Guideline:	EPA OTS 798.5300
Test Type:	Mouse Lymphoma Forward Mutation Assay
Year:	1979
GLP:	No
Method:	Phosflex 51B was evaluated for gene mutation in mouse lymphoma L5178Y cells in the presence and absence of an induced rat liver metabolic activating system. Negative control, solvent control (DMSO), positive controls and Phosflex 51B treated cells were cultured and then evaluated for mutagenic activity. Doses used in this test, 0.975, 15.6, 31.3, 62.5, and 125 nl/ml, were chosen based on the results of a preliminary cytotoxicity test.
Results:	Phosflex 51B did not induce gene mutations in mouse lymphoma L5178Y cells, either in the presence or absence of a metabolic activating system. The positive control chemicals induced a significant increase in gene mutations, confirming the sensitivity of the assay.
Conclusion:	Phosflex 51B did not demonstrate mutagenic activity in this assay.
Reliability:	1
Reference:	20

5.3.2 In Vitro Chromosome Aberrations

Identity:	Phosflex 51B (Lot No. 4833)

Guideline:	EPA OTS 798.5900
Test Type:	Mouse Lymphoma Cytogenetic Assay
Year:	1979
GLP:	No
Method:	Phosflex 51B was evaluated for the ability to cause chromosomal aberrations and/or sister chromatid exchanges in the mouse lymphoma cytogenetic assay, in the presence and absence of an induced rat liver metabolic activating system. A negative control, solvent control (DMSO), and positive control groups were included in the assay. Doses used in this assay, 0.625, 1.25, 2.50, 5.0, 10.0, and 20 nl/ml. were selected based on the results of a preliminary cytotoxicity assay.
Results:	Phosflex 51B did not induce chromosomal aberrations or sister chromatid exchanges in this assay. The positive control chemicals induced a significant incidence of cytogenetic mutations, confirming the adequacy and sensitivity of this assay.
Conclusion:	Phosflex 51B did not demonstrate mutagenic activity in this assay.
Reliability:	1
Reference:	21

5.4 Reproductive Toxicity

Identity:	Phosflex 61B (Lot No. 00161K0103 T#129B)
Guideline:	OECD 421 and EPA OPPTS 870.3550
Test Type:	Reproductive/Developmental Toxicity Study
Year:	2003
GLP:	Yes
Species:	Rat
Strain:	Sprague-Dawley
Method:	Twelve male and 12 female rats received Phosflex 61B by oral gavage daily for 2 weeks prior to mating, during the 2 week mating period, and through gestation and lactation. Doses administered were either 0 (vehicle control), 50, 250, or 1000 mg/kg/day. End points measured during the study include parental food consumption, body weight, body weight gain, reproductive performance, organ weights, and histopathology of the reproductive organs. Also evaluated were offspring body weights and survival, litter size, and the presence of gross anomalies.
Results:	The daily administration of Phosflex 61B to male and female rats did not result in clinical signs in toxicity, or in changes in food consumption, body weights, body weight gain, or in organ weights. There were no treatment-related histological changes in the reproductive organs. Further, there were no significant differences in litter size or the number of live pups on postnatal days 0 and 4. The NOAEL for reproductive toxicity is 1000 mg/kg/day.
Conclusion:	The NOAEL for reproductive toxicity is greater than 1000 mg/kg/day.
Reliability:	1

Reference:	22
Identity:	Commercial hydraulic fluid containing butylated triphenyl phosphate and other phosphate esters, obtained from a U.S. Navy Ship Yard
Guideline:	Not Applicable
Test Type:	Continuous Breeding Study
Year:	1993
GLP:	No
Species:	Rat
Strain:	Fischer 344
Method:	Milspec C, a commercially available hydraulic fluid containing butylated triphenyl phosphate and other phosphate esters, was administered to groups of Fischer 344 male and female rats in amounts necessary to achieve butylated tripenyl phosphate dose levels of 600, 1000, or 1700 mg/kg/day. Dosing was daily for up to 135 days. Parameters measured include mating efficiency and fertility, number of litters, estrus cycle, reproductive organ weights, liver weights, and parental and fetal body weights.
Results:	The mid and high dose animals expressed reduced fertility, prolonged estrus cycle, and a decreased mating index. A significant decrease in body weight gain in both mid and high dose females throughout the study , including a 10% loss of body weight in mid-dose females in the first week, suggests significant systemic toxicity may have been the primary cause of the decreased fertility. The MTD appears to have been exceeded in the female animals. There were no significant effects on reproductive performance in the male animals. Since the other components in the Milspec C were not specified, one cannot exclude the possibility that one or more components in the fluid other than the butylated triphenyl phosphate caused the decrease in fertility. Also, since the body weights of the mid-dose females were significantly lower than the body weights of the high dose females from about day 10 through day 131, a dosing error cannot be ruled out in this non-GLP study.
Conclusion:	The test substance used in this study contained unidentified components that may have been responsible for the decrease in fertility in the female animals. The study does not conclusively show butylated triphenyl phosphate to have reproductive toxicity.
Reliability:	3
Reference:	23

5.5 Developmental Toxicity/Teratogenicity

Identity:	Phosflex 51B (Lot No. EHC-0065-21)
Guideline:	EPA OTS 798.4900
Test Type:	Teratology Study
Year:	1982

GLP:	Yes
Species:	Rat
Strain:	Sprague-Dawley
Method:	Thirty pregnant rats per group received either 0, 100, 400, or 1000 mg/kg/day of Phosflex 51B by oral gavage from gestation day 6 through gestation day 20. Animals were observed daily for signs of treatment-related effects. Body weights and food consumption were measured on study days 0, 6, 9, 12, 16 and 21. The pregnant animals were sacrificed on gestation day 21. They underwent necropsy and gross internal examination. The liver from each dam was weighed. The reproductive tract was removed, weighed, and examined. The uterus was examined for the number and distribution of fetuses and resorptions. Ovaries were examined for corpora lutea, which were counted. All fetuses were weighed, sexed, and examined for external malformations. One half of the fetuses of each litter were fixed and stained for skeletal examination and the other half were fixed for visceral examination.
Results:	The dams expressed minimal clinical signs during treatment. In general, mean body weights of the treated rats were not significantly different from those of the control group. Five animals in the high dose group showed significantly reduced body weights between gestation days 6 - 16. The terminal body weights for these animals were not significantly different from control values. Food consumption was significantly reduced in the high dose animals. No treatment-related gross lesions were observed at necropsy. A significant increase in liver weights was observed in all treatment groups, showing a dose-response. This increase was considered an adaptive effect, rather than a toxic response to the chemical. Uterine weights were unaffected. There were no treatment-related effects on the number of corpora lutea, implants, resorption sites, or live fetuses per dam. Mean fetal weight for the high dose litters was significantly reduced by eight percent, a reduction most probably due to and secondary to maternal toxicity. There was no effect on litter size or fetal weights for the mid and low dose groups. There were no significant increases in external, soft tissue, or skeletal anomalies in any treatment group.
Conclusions:	The increased absolute and relative liver weights observed in all three treatment groups was considered an adaptive response (i.e., enzyme induction) and not a treatment-related toxicity. Treatment with Phosflex 51B during gestation did not result in developmental toxicity (teratogenicity).
Reliability:	1
Reference:	24

5.6 Neurotoxicity

Identity:	Phosflex 51B (Lot No. 4833-1-2)
Guideline:	EPA OTS Guideline for Acute Neurotoxicity Testing – 1978

Test Type:	Acute Delayed Neurotoxicity Test
Year:	1980
GLP:	No
Species:	Hen
Strain:	White Leghorn
Method:	Fifteen adult White Leghorn hens received a 11.7 g/kg dose of Phosflex 51B at the start of the study and again 21 days later. A group of 12 hens, comprising the negative (untreated) control group, received 10 ml/kg corn oil. Another group of 12 hens received two doses of 500 mg/kg of the positive control chemical, TOCP, 21 days apart. All hens were observed daily for clinical signs of neurotoxicity. Each hen was removed from its cage weekly and forced to walk on a horizontal surface to check for locomotor impairment (ataxia). All hens were terminated 3 weeks after the second dose. The animals were terminated with sodium pentobarbital, infused with neurtral buffered formalin, and the brain, spinal cord, and sciatic nerves were removed for histopathologic examination. In addition to H&E staining, sections from each tissue specimen were stained with Luxol Fast Blue and counterstained with periodic Acid Schiff stain.
Results:	All hens treated with Phosflex 51B or corn oil survived the entire study. Nine of the 12 TOCP treated hens survived. Body weights of the corn oil treated hens were not affected whereas the Phosflex 51B treated hens showed mild body weight loss. TOCP treated hens showed severe body weight loss. The clinical signs expressed by the Phosflex 51B treated hens were very similar to those shown by the negative control animals. Most of the TOCP treated hens showed leg weakness beginning on days 13-16 that increased in severity through the remainder of the study. Ataxia was very evident in this positive control group. Gait was unaffected in the negative control and Phosflex 51B treated hens. All three groups showed a decrease in egg production through the study. Distinct neurohistological changes of a degenerative nature were observed only in the positive control group. These changes included axonal swelling or degeneration with myelin fragmentation. Examination of the central and peripheral nerves from the Phosflex 51B and negative control hens showed background changes in both groups that were very similar in type, incidence and degree. Phosflex 51B administered to hens at the very high dose of 11.7 g/kg did not cause neurotoxicity. There was no evidence of motor impairment or TOCP-like nerve lesions in the Phosflex 51B treated hens.
Conclusion:	Phosflex 51B did not show neurotoxic activity.
Reliability:	1
Reference:	25
Identity:	Phosflex 51B (Lot No. 4833-1-2)
Guideline:	EPA OTS Guideline for Acute Neurotoxicity Testing – 1978
Test Type:	Acute Delayed Neurotoxicity Test
Year:	1980
GLP:	No

Species:	Hen
Strain:	White Leghorn
Method:	Three groups of White Leghorn hens, each consisting of 4 adult animals, received a single oral gavage dose of either corn oil (10 ml/kg), TOCP (45 mg/kg), or Phosflex 51B (10 ml/kg). Twenty-four hours after dosing the animals were sacrificed and plasma cholinesterase activity and brain neurotoxic esterase (NTE) activity were measured.
Results:	Both TOCP and Phosflex 51B produced significant inhibition of plasma cholinesterase activity. TOCP caused 47% inhibition whereas Phosflex 51B caused 56% inhibition of plasma cholinesterase activity. While TOCP inhibited NTE activity by 64%, Phosflex 51B did not inhibit NTE activity (0% inhibition). Although Phosflex 51B caused cholinesterase inhibition at the very high dose of 10 ml/kg (11.7 g/kg!!), there is no evidence that the substance causes cholinesterase inhibition at significantly lower doses, which would be more representative of levels of human exposure. No inhibition of NTE activity indicates Phosflex 51B will not cause delayed peripheral neurotoxicity.
Conclusion:	Phosflex 51B did not demonstrate neurotoxic activity.
Reliability:	2
Reference:	26

Identity:	Durad 220B
Guideline:	EPA OTS Guideline for Acute Neurotoxicity Testing – 1978
Test Type:	Acute Delayed Neurotoxicity Test
Year:	1992
GLP:	No
Species:	Hen
Strain:	Not stated
Method:	Durad 220B was evaluated for the potential to cause acute delayed neurotoxicity. Three groups of adult hens (9 hens per group) received a single oral dose of either Durad 220B (2 g/kg), tap water (1.7 g/kg) or TOCP (500 mg/kg). Brain and spinal cord neurotoxic esterase (NTE) activity and brain acetylcholinesterase activity was measured in 3 hens per group 48 hours after dosing. The remaining 6 hens per group were held through the 21 day observation period, sacrificed, at which time the brain, spinal cord, and peripheral nerves were removed from each animal for histopathological examination.
Results:	No inhibition of brain or spinal cord NTE activity or brain acetylcholinesterase activity was observed in Durad 220B treated hens. None of the Durad 220B treated hens exhibited clinical signs of neurotoxicity during the 21 day observation period following dosing. In contrast, clinical signs of neurotoxicity were evident in the TOCP hens. Histopathologic examination of the nerves from Durad 220B treated hens did not reveal axonal degeneration whereas the hens that received TOCP had degenerative axonal changes. Thus Durad 220B did not produce neurotoxicity when administered at a dose of 2 g/kg.
Conclusion:	Durad 220B did not express neurotoxic activity.

Reliability: 2
Reference: 27

Identity: Synthetic Jet Engine Oil containing 3% Butylated Triphenyl Phosphate
Guideline: EPA OTS Guideline for Neurotoxicity Testing – 1978
Test Type: Subchronic Delayed Neurotoxicity Test
Year: 1996
GLP: No
Species: Hen
Strain: White Leghorn
Method: A subchronic neurotoxicity study was conducted in adult White Leghorn hens to determine the neurotoxic potential of jet engine lubricants containing phosphate ester additives. Groups consisting of 20 animals each were gavaged daily with 1g/kg of one of four blends of jet engine turbo oil containing 3% of either tricresyl phosphate, triphenyl-phosphorothionate, or butylated triphenyl phosphate, 5 days per week, for up to 13 weeks. Another group received 7.5 mg/kg/day of TOCP, the positive control chemical. The hens were observed for clinical signs of neurotoxicity. After 6 weeks 4 hens from each group were sacrificed and used to determine brain and spinal cord acetylcholinesterase and neurotoxic esterase (NTE) activity. At the end of 13 weeks 4 hens per group were used for brain acetylcholinesterase and NTE activity measurements while the remaining 12 hens per group underwent histopathologic examination of the brain, spinal cord, and sciatic and tibial nerves.
Results: TOCP treated hens showed a progressive worsening of clinical symptoms (i.e., ataxia, diarrhea) during the observation period and an inhibition of brain and spinal cord NTE activity of 50% and 43% after 6 weeks and 76% and 50% after 13 weeks. There were no significant decreases in brain or spinal cord NTE activity in lubricant treated hens after 6 weeks treatment. After 13 weeks, hens treated with lubricant containing 3% butylated triphenyl phosphate showed a 32% and 27% decrease in brain and spinal cord NTE activity, respectively. Brain and spinal cord acetylcholinesterase activity was not inhibited in the butylated triphenyl phosphate treated hens. No histological lesions indicative of delayed neuropathy were seen in any of the lubricant treated hens whereas TOCP induced lesions characteristic of organophosphate-induced delayed neuropathy. The authors conclude that lubricant oils containing up to 3% butylated triphenyl phosphate have low potential to cause neurotoxicity.
Reliability: 2
Reference: 28

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